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13. ABSTRACT (Maximum 200 Words) The University of Alabama at Birmingham (UAB) Clinical Trial Network was formed with the aim of establishing a clinical research consortium between the UAB Comprehensive Cancer Center (UAB CCC), community-based oncology practices, and pharmaceutical sponsors, which would provide access to high priority breast cancer clinical trials to women in the community. The Department of Defense (DOD) grant provided funding to establish the network infrastructure followed by the activation of breast cancer clinical trials in the community. This was the first time ever implementation of this funding mechanism. Year 01 was primarily dedicated to establishment of the network infrastructure and development of a working relationship between the network and funding organization as well as the Human Subjects Research Review Board (HSRRB) in regards to protocol approval and activation. Six clinical trials were activated in Year 02 and accrued a total of 69 patients. Clinical trials at the network sites were put on hold in Year 03 following an Food and Drug Administration (FDA) audit of a non-network trial revealed deficiency in protocol compliance and Good Clinical Practice (GCP). A non-funded extension was approved for Year 04. A total of 121 patients were accrued at the network sites during the funding period and currently three protocols are actively accruing patients. The major accomplishments during the granting period included establishment of a successful clinical trials network that provided access to women in the community to cutting edge clinical trials. While the FDA-mandated clinical hold resulted in a substantial setback to the momentum of the network activity and a disruption of the proposed clinical research efforts, with the assistance of the academic partner, retraining and reorientation, the network sites successfully established a self-sustaining clinical research program and recently successfully passed an FDA audit. While the achievements did not meet the expectations of the <i>Scope of Work</i> , the long-term prospects of ongoing clinical research at the community level are excellent and provides validation for the need and relevance of this funding mechanism			
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Introduction

In 2000 we initiated a Clinical Trials Network linking the UAB CCC with a large community-based oncology group specifically for the purpose of conducting high priority breast cancer clinical trials at the community level. The intent was to establish a clinical trials infrastructure at the community level that would provide women with access to cutting edge clinical trials, including UAB CCC supported investigator initiated clinical trials.

The original network consisted of linkage to Georgia Cancer Specialists (GCS), a 23-clinic /35-physician Hematology-Oncology Group practice in metropolitan Atlanta with a patient base of 8,000 new patients per year and 20,000 patient visits per year. At the onset one clinic was selected as the pilot research site and patients were referred to this location for enrollment onto clinical trial. By the end of the funding period, the network had expanded to include 5 geographically, strategically located clinics sites that were within referral range of all 23 GCS clinics. Each research clinic was staffed by a subinvestigator, 2 clinical research coordinators (CRC) and 2 data managers. By the end of the funding period, a total of 9 clinical trials had been activated within the network for a total accrual of 121 patients. As a by- product of this network, 20 physicians, 10 research nurses and 8 data managers received training in the conduct of clinical trials, attended annual Institutional Review Board (IRB) sponsored human subject protection training and are now involved in an ongoing and self-sustaining community-based clinical research program. In addition, the network has recently been expanded to include a large community practice in Birmingham and Montgomery, Alabama.

Body

Year 1: Network infrastructure and initial of clinical trials:

- **Task 1: Recruitment, placement and training of research RN and DM at network locations specifically dedicated to high priority breast cancer clinical trials.**
Accomplished
- **Task 2: Regulatory/administrative approval and activation of the first three breast cancer network trials.** Because of divergent administrative and regulatory approval expectations between the UAB Institutional Review Board (IRB) and the Human Subjects Research Review Board (HSRRB), there was significant delay in the approval of the first network clinical trial. UAB 9912 was activated in August 2000. *Accomplished*
- **Task 3: Activation of UAB-CLINTRIP screening program at all network sites and incorporation of first generation breast cancer protocols in screening database.** This task was *accomplished* and all network sites have access to UAB-CLINTRIP for matching patients to network clinical trials. In view of the limited number of active protocols, manual screening by RNs has been found to be more effective at most network locations.
- **Task 4: Awareness/promotion of aims and goals of network among participating sites and network oncologists.** Patient accrual for network clinical trials are reviewed at the monthly GCS Research & Therapeutic meeting, and means to enhance awareness and accrual

are discussed at the weekly network research meeting. All network trials, accruals and solutions for accrual barriers are discussed at every quarterly physicians meeting. Ongoing

- **Task 5: Promotion of network concept and recruitment of patients for breast cancer trials to in collaboration with Susan G. Komen Breast Cancer Foundation and support groups.** The clinical trials were presented to breast cancer support groups. Although attractive in concept, promotion of clinical trials conducted by one specific community-based practice could not be promoted by support groups, especially given the fact that support group patients came from different community practices, and referral from one practice to the other within the community setting is exceedingly uncommon.
- **Tasks 6: Accrual and completion of phase I trial (#1).** In view of the delay in establishing an approval process between UAB IRB and HSRRB, the start of the proposed network clinical trials in Year 01 was delayed until Year 02.
- **Task 7: Accrual to one randomized phase II trial (#1).** Please see response to Task 6.
- **Task 8: Accrual to single arm phase II trial (#2).** Please see response to Task 6.

Year 2

- **Task 9: Completion of randomized phase II trial:** Phase I/II clinical trials initiated at UABCCC and projected to be conducted at network sites during Year 01 had to be pushed off into Year 02 due to administrative and regulatory requirement. As a consequence the project phase I and II mix could not be adhered to since some of the proposed network trials were closed to accrual by the time the network was ready for patient accrual. It will thus be observed that the initially projected protocol mix could not be adhered to during the subsequent funding period. It also became apparent that phase I clinical trials, which required close in-patient monitoring and pharmacokinetic studies could not be performed at the network sites in the absence of a General Clinical Research Center (GCRC) support. As such, the conduct of phase I clinical trials was hampered at the network sites and could not meet the expectations established by the *Scope of Work*. On the other hand large phase III clinical trials requiring large number of patients to establish new standards of care e.g. adjuvant therapy trials, were very attractive for the community based setting given the large number of accessible patients who were receiving adjunctive treatment in the community.

Our original *Scope of Work* did focus on early clinical trials and did not foresee the introduction of randomized phase III clinical trials in the network. However, given the circumstances surrounding delayed activation of early clinical trials in the network and availability of cutting edge randomized phase III adjunctive trials at the opportune moment, these were introduced at the network sites following network activation.

This resulted in distortion of the protocol mix initially proposed in our *Scope of Work* and was a major change from our original intent. This is reflected in our progress report. Following clearance of regulatory and administrative hurdles, the following clinical trials were introduced into the network and began accrual in Year 02:

Phase I Trial: UAB 0009 – A Phase I Clinical and Pharmacokinetic Evaluation of Oral CI-1033 Given as a Single Dose Daily in Patients with Advanced Nonhematologic Malignancies

Phase II Trial: UAB 9912 – A Phase I/II Study Using SGN-15 (cBR96-Doxorubicin Immunoconjugate) in Combination with TAXOTERE for the Treatment of Metastatic Breast and Colorectal Carcinoma

Phase II Trial: UAB 0152 – A Multicenter Phase 2 Study of CI-1040 in Patients with Advanced Nonsmall-Cell Lung Cancer, Breast Cancer, Colon Cancer, or Pancreatic Cancer

Phase III Trial: UAB 0047 – A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC) Versus Doxorubicin and Cyclophosphamide (Followed by Docetaxel (AC→T) as Adjuvant Treatment of Operable Breast Cancer HER2NEU Negative Patients with Positive Axillary Nodes

Phase III Trial: UAB 0106 – Multicenter Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC→T) with Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (AC→TH) and with Docetaxel, Platinum Salt and Trastuzumab (TCH) in the Adjuvant Treatment of Node Positive and High Risk Node Negative Patients with Operable Breast Cancer Containing the HER2NEU Alteration

The Year 02 accruals for these trials are provided in Table 1.

- **Task 10: Completion of phase II trial (#2).** Please see responses to Task 9.
- **Task 11: Review and analysis of Year 01 activities with internal and external advisory committees.** The review and analysis of Year 01 activity by the advisory board led to the realization of the limitation in conducting complex early phase I clinical trials in the community setting and the need to reevaluate the protocol mix that could be exported through network sites. It was felt that network sites would be most suited for the conduct of phase II studies that followed the achievement of the maximum tolerated dose (MTD) in phase I trials. The advisory board also recommended that phase III trials be conducted at network sites given the number of eligible patients and the opportunity to provide women in the community access to novel therapeutics.
- **Task 12: Initiation and accrual to two new phase I clinical trials (#2, #3).** Please see response to Task 9.
- **Task 13: Initiation and accrual of two new phase II clinical trials (#2, #3).** Please see response to Task 9.
- **Task 14: Completion of phase I trial (#2).** Please see response to Task 9.

- **Task 15: Completion of phase I trial (3#).** Please see response to Task 9.

Year 3

Task 16: Review and analysis of Year 01-02 activities with external and internal advisory committee. In May 2002 an FDA audit revealed non-compliance and GCP deviation of a non-network clinical trial protocol. The non-network clinical trial was placed on hold by the FDA. In response to these findings, GCS in consultation with UAB CCC, introduced a self-imposed moratorium on activation of all new protocols and accrual of any new patients, in order to thoroughly investigate areas of GCP deficiency and put into place a corrective action plan. In concert with UAB CCC the entire clinical research staff underwent a re-orientation and retraining in clinical trial conduct, human subject protection, protocol compliance, and GCP.

In view of this occurrence and the potential liability to UAB CCC placed by non-compliance and FDA action triggered by a non-network clinical trial, the internal and external advisory board suggested a revision of the clinical trial network project. In addition, UAB IRB in response to the FDA action placed stricter criteria for the approval of clinical trials conducted at the network sites. This led to a major revision of the network agreement between UAB CCC and GCS resulting in stricter administrative and regulatory requirement for study activation and increased regulatory compliance and oversight measure. This episode and the ensuing fall-out, while very important in establishing GCP at the network sites, led to significant drop in the momentum at the network sites.

Following regulatory clearance and sign-off by pharmaceutical sponsors, network trials were reinitiated in the later part of Year 03 with continuation during the no-cost extension of the grant. A no-cost extension of the grant was approved by the DOD to allow completion of previously initiated projects and activation of new projects under the revised guidelines established by UAB CCC and UAB IRB.

Following the 6 month moratorium clinical trials at network sites was resumed following successful audit both by an internal and independent external auditors.

The two phase III trials (UAB 0047 and UAB 0106) initiated in Year 02 and still open to accrual were restarted in Year 03 and accrued a total of 23 patients (**Table 1**). In view of restrictions place by UAB IRB and a wait and watch attitude adopted by pharmaceutical sponsors, no additional trials were initiated during Year 03. A second FDA audit of a non-network trial in late Year 03 revealed no major deficiencies and noted compliance with the corrective action plan that had been put in place following the first audit. The prior FDA clinical hold was lifted thus allowing the network sites to resume unrestricted clinical trial conduct.

This unanticipated occurrence coupled with the change in clinical trial repertoire offered at the network during Year 02 led to a significant alteration from the original *Scope of Work* in Year 03.

Task 17: Completion of phase II trials #3, #4. Please see response to Task 16.

Task 18: Initiation and completion of two phase I trials (#4, #5). Please see response to Task 16.

Task 19: Initiation and accrual to two new phase II trials (#5, #6). Please see response to Task 16.

Year 4

A no-cost extension was approved to complete ongoing clinical trials still active in Year 03 and to allow activation of new planned clinical trials. UAB 0047 and UAB 0106 were carried forward from Year 03 and accrued 19 patients in Year 04 before being closed to accrual. During this period 3 additional breast cancer clinical trials were initiated at the network sites. The 2 two-stage multicenter phase II trials (*GSK 3001: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Phase III Study of Oral GW572016 in Combination with Paclitaxel in Subjects previously Untreated for Advanced or Metastatic Breast Cancer* and *GSK 30008: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study Comparing GW572016 and Letrozole versus Letrozole in Subjects with Estrogen/Progesterone Receptor-Positive Advanced or Metastatic Breast Cancer*), which accrued a total of 8 patients before being placed on hold by the sponsor for interim analysis. Both trials continue to be on hold awaiting outcome of the interim response analysis. A randomized phase III clinical trial (*Biomed 777-CLP-29: Phase III Study of Atamestane Plus Toremifene versus Letrozole in Advanced Breast Cancer*) was also initiated and has accrued 2 patients and is currently ongoing.

The network has also been approved to conduct a large international multicenter phase III breast cancer prevention trials (*NCIC CTG Trial: Map.3: A Phase III Randomized Study of Exemestane Plus Placebo versus Exemestane Plus Celecoxib versus Placebo in Postmenopausal Women at Increased Risk of Developing Breast Cancer*), which has recently been activated and is ongoing.

Table 1

Clinical Trials	Accrual				Total
	2000	2001	2002	2003-04	
01	02	03	04		
UAB 9912 (phase II)	0	17	0	0	17
UAB 0009 (phase I)	0	4	0	0	4
UAB 0152 (phase II)	0	16	0	0	16
UAB 0028 (phase III)	0	12	0	0	12
UAB 0047 (phase III)	0	20	16	3	39
UAB 0106 (phase III)	0	0	7	16	23
GSK 3001 (phase II)	0	0	0	5	5
GSK 30008 (phase III)	0	0	0	3	3
Biomed 777 (phase III)	0	0	0	2	2
NCIC CTG Trial: Map.3	0	0	0	0	2
Total	0	69	23	29	121

Key Research Accomplishments:

While falling short of its stated goals and scope of work, a number of key research accomplishments were achieved during this funding period:

- Establishment of a community-based clinical trial network which has resulted in the engagement of the largest community based oncology practice in the southeast to actively participate in clinical research. Despite falling short of the originally proposed *Scope of Work*, a total of 9 clinical trials were activated and accrued 121 patients during the funding period.
- As a result of the research infrastructure and initiation of network clinical trials during the funding period, GCS continues to actively participate in clinical research and now has a self-sustaining and GCP compliant research program, offering patients in the community access to clinical protocols. The active engage of UABCCC following the FDA audit enabled the network to salvage its research organization and reestablish itself as a long term clinical research partner.
- While the achievements over the past 3 years and the subsequent no-cost extension in Year 04 did not yield the anticipated early clinical trial activity or the patient accrual numbers for breast cancer trials, and fell short of most of its original *Scope of Work*, the network partner has established a clinical research program that would not have been feasible without the grant support and today has an active interaction with UAB CCC and pharmaceutical sponsors.
- As a result of the experience during the funding period UAB CCC has revised the network infrastructure and has established new guidelines for the recruitment of network partners in order to ensure conduct of clinical research under GCP guidelines. As a result, the funding mechanism has yielded tangible benefit in promoting community-based clinical research at a number of community sites that would otherwise not participate in clinical trials. Patients at the community level have in turn been able to gain access to clinical trials.
- 20 clinicians, 10 clinical research coordinators and 8 data managers have undergone clinical trial methodology and GCP training and are capable of actively participating in the conduct of clinical trials and contribute to the delivery of compliant protocol care to patients in the community. All of these individual continue to be actively engaged in the performance of clinical trials in the community.

Reportable Outcomes

- **Presentations at ASCO 2003**

Hart LL, Nabell L, Saleh M, Sundaram S, Mauer A, Marshall J, McCune D, Sandler AS, Sing AP, Siegall C: A phase II study of SGN-15 (cBR96-doxorubicin Immunoconjugate) combined with docetaxel for the treatment of metastatic breast carcinoma. *American Society of Clinical Oncology 38th Annual Meeting*, May 31-June 3, 2003. Abstract #696

Saleh MN, Irwin D, Burton G, Hargis JB, Chitambar C, Jones CM, Shapiro CL, Holmlund JT, Dorr A: Phase 2 trial of ISIS 2503, an antisense inhibitor of h-ras, in combination with weekly paclitaxel in the treatment of patients with metastatic breast cancer. *American Society of Clinical Oncology 38th Annual Meeting*, May 31-June 3, 2003. Abstract #829

Of the 9 clinical trials conducted in the network, GCS is one of the top five accruing site for 2 phase III clinical trials (UAB 0047 and UAB 0106) and 1 phase II clinical trial (GSK 01) thus ensuring authorship on a future publication.

Conclusion

The UAB Clinical Trials Network was established as a unique setup for the conduct of both early phase I/II and phase II trials using novel agents in the community setting. While the patient base to support such an endeavor exists and patients in the community are very willing to participate in clinical trials, the experience during the funding period has provided a measure of realism and revealed some of the difficulties encountered in conducting clinical trials in the community and operating a clinical trials network between an academic Cancer Center and a busy community-based oncology practice. The need for trained research personnel as well as genuine commitment and compliance on part of community-based research programs and the limitation to the kind of clinical trials that can be adequately conducted in the community was a major lesson learned.

While the goals and objectives proposed in our study were not entirely met, it is fair to say that the “return on investment” in terms of patient accrual, training of a cadre of dedicated clinicians, clinical nurse coordinators and data manager at the network, all of whom continue to be actively involved in clinical trials, as well as protocol compliance and adherence to GCP achieved during the course of the funding period is a major achievement of the projected *Scope of Work* and validates the funding of such proposals. Despite the inability to achieve the proposed *Scope of Work*, the funding mechanism has lead to a cadre of dedicated investigators and support staff who remain committed to the conduct of clinical research. This has resulted in an active clinical research program at the network sites. This will ultimately benefit patients in the community, who are able to access and participate in clinical trials within the community, and who otherwise would be lost to participation and contribution to the progress of clinical research.

References

N/A

Appendices

N/A